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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,721	02/09/2004	Ralf Jockers	FRAV2003/0005USNP	9535

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EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
01/02/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/774,721	JOCKERS ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,14,15,17 and 47-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12, 14, 15, 17, and 47-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 10/31/2008 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 5/2/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 10/31/2008, claims 12, 14, 15, 17, and 47-54 are pending and examined herein. The amendment adds new claims 49-54.

Claim Rejections - 35 USC § 112, first paragraph (New matter)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claims 49-54 are drawn to an interfering RNA comprising SEQ ID NO:2.

MPEP 2163, Section II, Part A, states in part that there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed,

Wertheim, 541 F.2d at 262, 191 USPQ at 96; however, with respect to newly added or amended claims, applicant should show support in the original disclosure for the new or amended claims. The purpose of the written description requirement is "to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him." MPEP 2138.05, I.

In the instant case, adequate written description support is not found in the instant application for an interfering RNA comprising SEQ ID NO:2. In presenting claims 49-54 for examination, Applicant points to the original claims, page 36 of the specification, and page 2 of the sequence listing. The cited passages have been reviewed. The Examiner finds no description therein of any iRNA comprising SEQ ID NO:2.

Reviewing the specification in its entirety, the Examiner finds at page 3 and 8 that SEQ ID NO:2 is disclosed only as an antisense oligonucleotide, not an interfering RNA. In its description of iRNAs targeted SEQ ID NO:21, the specification states at page 8 that such iRNAs comprise 17 or 19 nucleotides taken continuously from the sequence SEQ ID No. 21, or from the sequence complementary thereto. Preferred iRNAs are those that comprise a sequence exhibiting at least 60% identity with SEQ ID No. 37 or 38. Hairpin iRNAs are also disclosed with one preferably comprising SEQ ID NO:42 (page 9). See also Fig. 11 and page 25. However, none of these preferred iRNAs comprise a sequence identical to SEQ ID NO:2, and the general disclosure teaching an iRNA may be targeted to SEQ ID NO:21 is not descriptive of any particular individual iRNA such as that specifically comprising SEQ ID NO:2. Thus, while the specification adequately supports claims to an antisense oligonucleotide comprising SEQ ID NO:2, it does not support claims to an iRNA (i.e., double stranded RNA) comprising SEQ ID NO:2. Obviousness cannot be relied on

for written description support, and the Examiner fails to find any implicit or inherent support for the claims as now written.

Thus, one of skill would not recognize applicant was in possession of the invention defined by claims 49-54. Accordingly, the instant claims as a whole are rejected for lack of written description support.

The Examiner further notes claims 49-54 recite an invention distinct from that originally elected. See response filed 7/28/2005, wherein Applicant elected the iRNA comprising SEQ ID NO:37. Because Applicant received an Action on the merits with regard to the iRNA of SEQ ID NO:37, that invention has been constructively elected. However, at the Examiner's discretion the new claims have been entered, searched, and examined. However, Applicant is reminded that the Office normally does not permit Applicant to switch inventions (MPEP 821.03), and any future claims drawn to iRNA agents distinct from those examined to date would be withdrawn as being directed to a non-elected invention, pursuant to the original Restriction Requirement mailed 6/15/2005, since searching and examining multiple distinct sequences in a single application imposes a serious burden on the Examiner. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 103

Claims 12, 14, 15, 17, 47, and 48 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bailleul et al. (US Patent Application 2003/0166847); Agrawal and Tang (WO 94/01550); Taylor et al. (1999) *Drug Discovery Today* 4:562–567; Bennet et al. (US Patent 5,998,148); and Baracchini et al. (US Patent 5,801,154).

Bailleul et al. (US Patent Application 2003/0166847) teaches a 874-bp cDNA sequence (SEQ ID NO:2; Figs. 1A-B) encoding human leptin receptor gene-related protein, or LRGRP, that is 99.4% identical to the first 874 base pairs of SEQ ID NO:21 of the instant application.

Bailleul et al. further teach the use of antisense DNA, RNA, or PNA molecules, antagonists, or inhibitors to LRGRP in pharmaceutical compositions for treatment of diseases associated with the expression of LRGRP (paragraphs 128–160 and 191–192, for example).

Bailleul et al. also teach the use of art-recognized methods for expressing antisense molecules from vectors and methods for introducing said vectors into cells (paragraphs 128-138). For example, at paragraph 136 it is taught that "…RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding LRGRP. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, antisense cDNA constructs that synthesize antisense RNA constitutively or inducibly can be introduced into cell lines, cells or tissues." In addition to antisense oligonucleotides targeted to the LRGRP gene, Bailleul et al. taught pharmaceutical compositions thereof, vectors, and methods for expressing antisense oligonucleotides in cells (paragraphs 128-138). Therefore, one of skill would immediately recognize that Bailleul et al. necessarily also taught the vector-containing and cell-based compositions thereof used for and produced by such applications. Thus, dependent claims 14, 15, 27, 47, and 48 do not patentably distinguish the base invention over that disclosed in the prior art.

US Patent Application 2003/0166847 goes on to teach (paragraph 192) that "An oligonucleotide based on the coding sequence of LRGRP, as shown in FIGS. 1A and 1B, is used to inhibit expression of naturally occurring LRGRP. The complementary oligonucleotide is

designed from the most unique 5' sequence as shown in FIGS. 1A and 1B and used either to inhibit transcription by preventing promoter binding to the upstream nontranslated sequence or translation of an LRGRP-encoding transcript by preventing the ribosome from binding. Using an appropriate portion of the leader and 5' sequence of SEQ ID NO:2, an effective antisense oligonucleotide includes any 15-20 nucleotides spanning the region which translates into the signal or early coding sequence of the polypeptide as shown in FIGS. 1A and 1B." Thus, US Patent Application 2003/0166847 teaches that the 5' end of the LRGRP, the end that is 99.4% identical to SEQ ID NO:21 of the instant application, should be used to design antisense molecules that will specifically hybridize with and inhibit LRGRP. Additionally, Bailleul et al. teach that a vector capable of expressing LRGRP, or a fragment or a derivative thereof, may also be administered to a subject to treat certain metabolic, reproductive, or developmental disorders, and that in those conditions where leptin receptor gene-related protein activity is not desirable, cells could be transfected with antisense sequences of LRGRP-encoding polynucleotides or provided with inhibitors of LRGRP (paragr. 98-99).

Bailleul et al. (US Patent Application 2003/0166847) does not teach the use of double stranded RNA as an inhibitor of LRGRP.

Agrawal and Tang teach self-stabilized, hairpin (i.e., double stranded) RNAs that form stable duplexes, resist nucleolytic degradation and activate RNase H, without the disadvantages of oligonucleotides known in the art. (page 3 and 19, and see Figs. 1, 5, and 6). For example, at page 5, Agrawal and Tang teach that "The advantages of oligonucleotides according to the invention, known as self-stabilized oligonucleotides, arise from the presence of two structural features: a target hybridizing region and a self-complementary region. The target hybridizing

region comprises an oligonucleotide sequence that is complementary to a nucleic acid sequence that is from a plant or animal virus, a pathogenic organism, or a cellular gene or gene transcript, the abnormal gene expression or product of which results in a disease state. The self-complementary region comprises an oligonucleotide sequence that is complementary to a nucleic acid sequence within the oligonucleotide. Thus, at least when the oligonucleotide is not hybridized to a target nucleic acid sequence, the oligonucleotide forms a totally or partially double stranded structure that is resistant to nucleolytic degradation. [...] This results in oligonucleotides that activate RNase H, an important feature for the antisense therapeutic compound."

Agrawal and Tang further teach that the "... target hybridizing region is from about 8 to about 50 nucleotides in length" (page 9-10); that "In a preferred embodiment, there are about 10 intramolecular base-pairs formed in the self-stabilized oligonucleotide, with the 10 base pairs being consecutive and involving the 3'-most nucleotides. Of course, the intra-molecular base-pairing can be so extensive as to involve every nucleotide of the oligonucleotide. Preferably, this will involve a self-complementary region of about 50 nucleotides or less." (page 15); and that the "...target hybridizing region of oligonucleotides according to the invention may contain ribonucleotides, deoxyribonucleotides or any analogs of ribonucleotides or deoxyribonucleotides." (page 13). On page 10, it is stated that "For purposes of the invention, the term "oligonucleotide sequence that is complementary to a nucleic acid sequence" is intended to mean an oligonucleotide sequence (2 to about 50 nucleotides) that hybridizes to the nucleic acid sequence under physiological conditions,e.a., by Watson-Crick base paring (interaction between oligonucleotide and single-stranded nucleic acid) or by Hoogsteen base pairing.

(interaction between oligonucleotide and doublestranded nucleic acid) or by any other means. Such hybridization under physiological conditions is measured as a practical matter by observing interference with the function of the nucleic acid."

It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to use the cDNA sequence of Bailleul et al. (US Patent Application 2003/0166847) to generate antisense sequences, vectors, pharmaceutical compositions, and transfected cells as taught by Bailleul et al. (US Patent Application 2003/0166847) for inhibition of LRGRP expression.

In addition, because the cDNA sequence (SEQ ID NO:2) taught by Bailleul et al. in US Patent Application 2003/0166847 is 99.4% identical to the first 894-bp at the 5' end of SEQ ID NO:21 of the instant application, antisense oligos targeting and specifically hybridizing to the Bailleul et al. sequence would be expected to also target and specifically hybridize to SEQ ID NO:21 of the instant application, possibly leading to inhibition of expression of SEQ ID NO:21.

One would have been motivated to create such antisense compounds because US Patent Application 2003/0166847 expressly teaches that LRGRP is expressed in several cancer cell lines and tumor tissues (paragr. 96). Therefore, antagonists of LRGRP may either indirectly or directly interfere with tumor cell growth. Such cancers may include, but are not limited to, adenocarcinoma, sarcoma, leukemia, lymphoma, and cancers of the brain, breast, and bladder. Furthermore, it is suggested that an antagonist such as an antisense oligomer of LRGRP may be administered to a subject to treat a connective tissue disorder. Such disorders include, but are not limited to, rheumatoid arthritis and Sjogren's syndrome (paragr. 97).

One would have been motivated to make and use double stranded antisense compounds as taught by Agrawal and Tang because they teach that self-stabilized, or hairpin RNAs have greater resistance to nuclease degradation. Due to their longer half life, Agrawal suggests that lower effective dosages will be needed for therapeutic efficacy (page 19). This provides the advantages of increased duplex stability and RNase H activation, which are not both provided by any nuclease resistant oligonucleotide known in the art.

Finally, one would have had a reasonable expectation of success of making functionally active antisense oligos that specifically hybridize to and inhibit the expression of SEQ ID NO: 21 of the instant application given the teachings of US Patent Application 2003/0166847, described above, and given that Taylor et al. teaches that antisense oligonucleotides 7-30 nucleotides long can be synthesized to inhibit the expression of any protein provided the cDNA sequence is known, that making and using such oligos are available to those of ordinary skill in the art, that it is common practice to chemically modify the such oligonucleotides to prolong their bioactivity, and that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% (p. 565).

Additionally, success and motivation would be expected in view of the teachings of Baracchini *et al.* (US Patent 5,801,154), who teach that antisense oligonucleotides can be used for research purposes. Baracchini *et al.* also teaches at column 8 that antisense oligonucleotides are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length. Baracchini is considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

The teachings of Bennett *et al.* (US Patent 5,998,148) are considered to parallel those of Baracchini *et al.* Bennett *et al.* teaches general antisense targeting guidelines at columns 3-4. Bennett *et al.* also teaches targeting 5'-untranslated regions, start codons, coding regions, and 3'-untranslated regions of a desired target. Bennett teaches, in column 5, for example, that antisense compounds are commonly used as research reagents and diagnostics. Column 5 indicates that antisense oligonucleotides 8-30 nucleotides in length are particularly preferred. Columns 10-24 teach numerous "carriers" for antisense oligonucleotides. Thus, Bennett *et al.* is also considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.

Thus, Baracchini *et al.* and Bennett *et al.* both teach making modified antisense compounds targeted to distinct regions of a target gene, the steps of which are routine to one of ordinary skill in the art.

Thus, in the absence of evidence to the contrary, the invention as a whole, as claimed in the instant claims, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

In the reply filed 10/31/2008, Applicant amends the claims to require the iRNA be double stranded and argues the claims do not embrace short hairpin (or self-complementary) RNAs of the type disclosed by the applied references, citing extrinsic evidence and arguing that "double helical" is not the same as "double stranded." The Examiner respectfully disagrees. For purposes of this examination, the limitation "double stranded", especially in the context of an iRNA agent, is considered to be synonymous with the double helical structure found in any

polyribonucleotide molecule or molecules containing intramolecular or intermolecular base-pairs. Certainly, there is no definition in the specification clearly excluding this interpretation, and the disclosure cited by applicant does teach that double stranded is different from double helical. While Applicant may find disclosure in the art allegedly supporting the contention that double stranded does not include hairpins, the Examiner could cite an equal number of patents, patent applications, and peer reviewed journal articles that expressly define interfering RNAs to include both conventional (bimolecular) structures as well as hairpin structures. Both have been shown to produce effects consistent with RNA interference. Furthermore, the preamble of instant claim 12 recites "An interfering ribonucleic acid (iRNA) oligonucleotide" (underline added). Thus, "oligonucleotide is in the singular form, which might normally be taken to mean a single strand of RNA, not two separate strands as applicant argues the claim is limited.

Accordingly, Applicant's arguments are not persuasive. The claims reasonably embrace both hairpin and non-hairpin type RNAs. It is respectfully suggested that if Applicant wishes to exclude hairpin RNAs from the scope of the claims, Applicant do so explicitly, using language that makes it clear the claimed iRNA consists of two separate sense and antisense strands that are not covalently linked to one another. Appropriate changes to the preamble statement would also be necessary. Such language if incorporated into the base claim and fully supported by the application as filed, would overcome the instant rejection.

Claim Rejections - 35 USC § 103

Claims 12, 14, 15, 17, 47, and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bailleul et al. (1997) *Nucleic Acids Res.* 25:2752-2758 in view of Tuschl et al.

(US 2004/0259247 A1), Shi et al. (US 20030180756 A1), and Hannon (2002) *Nature* 418:244-251.

Bailleul et al. taught the mRNA (gene) sequence encoding human leptin receptor gene-related protein, OB-RGRP (Fig. 1). The sequence, deposited into GenBank as Accession No. Y12670 and available online as of 15 July 1997, is identical to instantly recited SEQ ID NO:21, as shown by the alignment below.

Bailleul et al. taught that OB-RGRP mRNA is expressed in several human tissues (page 2755). Bailleul et al. suggest OB-RGRP mRNA could encode a protein involved in leptin signaling (page 2757,right column, bottom). It is said that leptin and leptin receptor play key roles in the regulation of body weight (page 2752, left column, first sentence).

Bailleul et al. do not teach interfering RNA targeted to OB-RGRP mRNA, nor vectors thereof.

Tuschl et al. taught methods and materials for making and using short interfering RNAs (siRNAs) of 21 to 23 nucleotides in length for inhibiting the expression of any known gene in mammalian cells in vitro and in vivo for research and therapeutic purposes (see specification, pp. 1-16). It is taught siRNAs are useful for determining the function of a gene in a cell or organism (paragraph 29-30, for example). Also disclosed are compositions comprising said interfering RNAs (paragraphs 31-33). Exemplary embodiments describing and illustrating RNA interference in mammalian cells are also disclosed (Fig. 10, paragraph 146). Tuschl et al. suggest that short interfering RNAs may be expressed from vectors upon delivery into cells (paragraph 39).

Shi et al. taught plasmid and viral-based vectors for stably expressing short hairpin RNA in mammalian cells in vitro and in vivo for the RNAi-mediated inhibition of any known gene

(pp. 1-9 and Fig. 1, for example). The method is expressly designed to facilitate the delivery and stable, endogenous expression of short interfering RNAs of the type taught by Tuschl et al. (page 1). Also disclosed are cells and compositions comprising said shRNA-expression vectors (paragraph 13, pages 18-20, and Examples 4-6, pages 22-25).

Accordingly, each of the elements of the instantly claimed invention are disclosed in the prior art. The prior art specifically recommends using siRNA and shRNA, transfected directly or expressed endogenously from vector constructs, as research tools to investigate gene function in mammalian cells. The shared properties and general utilities of siRNA and shRNA were explicitly taught by Hannon (2002) *Nature* 418:244-251, who stated in 2002 that "RNAi has evolved into a powerful tool for probing gene function" (page 250). Hannon goes on to state that Tuschl and colleagues showed that by using siRNA, RNAi could be extended to mammalian cells. Hannon states further that by employing stable expression constructs such as those disclosed by Shi et al., RNAi may be used to induce phenotypic changes in cells in vitro and in vivo (page 250). Thus, it is clear that RNAi was considered by the prior art to represent an effective and generally applicable experimental tool for probing gene function and manipulating gene expression in cells and organisms.

Additionally, the sequence corresponding to SEQ ID NO:21---the mRNA encoding OB-RGRP---was known in the prior art. Moreover, there was reason to suspect its involvement in leptin signaling and body weight regulation. But even without such knowledge, there would have been implicit reason to investigate the biology of the sequence corresponding to SEQ ID NO:21, identified by Bailleul et al. as OB-RGRP, given that it is the normal desire of scientists to understand the biological role of each gene and translation product in the human genome. RNAi,

a readily accessible and easily used method for silencing gene expression, was a well-established tool at the time of invention for investigating gene function.

It would therefore have been obvious to one of skill in the art at the time of invention to make and use siRNAs complementary to any known gene, including the OB-RGRP gene, SEQ ID NO:21, disclosed by Bailleul et al. One of skill would have been motivated to use the siRNAs to investigate the function of OB-RGRP in human cells and tissues, as generally directed by Tuschl et al. One of skill would have reasonably expected that the methods of Tuschl et al. and Shi et al. for making and using siRNAs and shRNA expression vectors could be applied to the study of OB-RGRP function, that the siRNAs and shRNA-expression vectors designed and prepared by such methods could be used to effectively inhibit OB-RGRP expression in cells in vitro and in vivo, and that such inhibition would yield information directly relevant to the function of said protein and gene. Given that the full-length sequence of OB-RGRP mRNA was known at the time of invention, and that Tuschl et al. and Shi et al. both taught the principles and methods for designing functional siRNAs (see siRNA User Guide in Tuschl et al., for example, at paragraph 178-181), the skilled artisan would have had a reasonable expectation of success in making and using said siRNAs and shRNAs for inhibition of OB-RGRP.

Furthermore, all the claimed elements---the methods and materials for making and using siRNAs, shRNA expression vectors, host cells, and compositions thereof, and the OB-RGRP mRNA target sequence---were known in the prior art. One skilled in the art could have combined the elements by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results (i.e., inhibition of OB-RGRP expression) to one of ordinary skill in the art. *KSR*, 550 U.S. at ___, 82 USPQ2d at 1395.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

```
LOCUS     HSOBRGRP        1114 bp   mRNA   linear   PRI 09-SEP-2004
DEFINITION  Homo sapiens mRNA for leptin receptor gene-related protein.
ACCESSION   Y12670
VERSION     Y12670.1  GI:2266637
KEYWORDS    leptin receptor gene-related protein; OB-R gene related protein;
            OB-RGRP.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini;
            Catarrhini; Hominidae; Homo.
REFERENCE   1
  AUTHORS   Bailleul,B., Akerblom,I. and Strosberg,A.D.
  TITLE     The leptin receptor promoter controls expression of a second
            distinct protein
  JOURNAL   Nucleic Acids Res. 25 (14), 2752-2758 (1997)
   PUBMED   9207021
REFERENCE   2  (bases 1 to 1114)
  AUTHORS   Bailleul,B.R.P.
  TITLE     Direct Submission
  JOURNAL   Submitted (17-APR-1997) B.R.P. Bailleul, UPR 0415 CNRS, 22 Rue
            Mechain, 75014 Paris, FRANCE
COMMENT     This is a splice variant from the leptin receptor locus but this
            variant encodes for a unrelated leptin receptor protein transcribed
            from one promoter of the leptin receptor locus.
FEATURES             Location/Qualifiers
     source          1. .1114
                     /organism="Homo sapiens"
                     /mol_type="mRNA"
                     /db_xref="taxon:9606"
                     /chromosome="1"
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                     /dev_stage="adult"
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                     /gene="OB-RGRP"
     mRNA            join(1114)
                     /gene="OB-RGRP"
     exon            1114
                     /gene="OB-RGRP"
                     /number=4
ORIGIN
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  Query Match             100.0%;  Score 1114;  DB 5;  Length 1114;
  Best Local Similarity   100.0%;  Pred. No. 0;
  Matches 1114;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 GTCTGGCTTGGGCAGGCTGCCCGGGCCGTGGCAGGAAGCCGGAAGCAGCCGCGGCCCCAG 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 GTCTGGCTTGGGCAGGCTGCCCGGGCCGTGGCAGGAAGCCGGAAGCAGCCGCGGCCCCAG 60

Qy         61 TTCGGGAGACATGGCGGGCGTTAAAGCTCTCGTGGCATTATCCTTCAGTGGGGCTATTGG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 TTCGGGAGACATGGCGGGCGTTAAAGCTCTCGTGGCATTATCCTTCAGTGGGGCTATTGG 120

Qy        121 ACTGACTTTTCTTATGCTGGGATGTGCCTTAGAGGATTATGGCGTTTACTGGCCCTTATT 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 ACTGACTTTTCTTATGCTGGGATGTGCCTTAGAGGATTATGGCGTTTACTGGCCCTTATT 180

Qy        181 CGTCCTGATTTTCCACGCCATCTCCCCCATCCCCCATTTCATTGCCAAAAGAGTCACCTA 240
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Db        181 CGTCCTGATTTTCCACGCCATCTCCCCCATCCCCCATTTCATTGCCAAAAGAGTCACCTA 240

Qy        241 TGACTCAGATGCAACCAGTAGTGCCTGTCGGGAACTGGCATATTTCTTCACTACTGGAAT 300
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Qy        301 TGTTGTTTCTGCCTTTGGATTTCCTGTTATTCTTGCTCGTGTGGCTGTGATCAAATGGGG 360
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Qy        361 AGCCTGCGGCCTTGTGTTGGCAGGCAATGCAGTCATTTTCCTTACAATTCAAGGGTTTTT 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 AGCCTGCGGCCTTGTGTTGGCAGGCAATGCAGTCATTTTCCTTACAATTCAAGGGTTTTT 420
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Qy        421 CCTTATATTTGGAAGAGGAGATGATTTTAGCTGGGAGCAGTGGTAGCACTTTATTCTGAT 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 CCTTATATTTGGAAGAGGAGATGATTTTAGCTGGGAGCAGTGGTAGCACTTTATTCTGAT 480

Qy        481 TACAGTGCATTGAATTTCTTAGAACTCATACTATCTGTATACATGTGCACATGCGGCATT 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 TACAGTGCATTGAATTTCTTAGAACTCATACTATCTGTATACATGTGCACATGCGGCATT 540

Qy        541 TTACTATGAAATTTAATATGCTGGGTTTTTTAATACCTTTATATATCATGTTCACTTTAA 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 TTACTATGAAATTTAATATGCTGGGTTTTTTAATACCTTTATATATCATGTTCACTTTAA 600

Qy        601 GAAAGACTTCATAAGTAGGAGATGAGTTTTATTCTCAGCAAATAGACCTGTCAAATTTAG 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 GAAAGACTTCATAAGTAGGAGATGAGTTTTATTCTCAGCAAATAGACCTGTCAAATTTAG 660

Qy        661 ATTATGTTACTCAAATTATGTTACTTGTTTGGCTGTTCATGTAGTCACGGTGCTCTCAGA 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        661 ATTATGTTACTCAAATTATGTTACTTGTTTGGCTGTTCATGTAGTCACGGTGCTCTCAGA 720

Qy        721 AAATATATTAACGCAGTCTTGTAGGCAGCTGCCACCTTATGCAGTGCATCGAAACCTTTT 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        721 AAATATATTAACGCAGTCTTGTAGGCAGCTGCCACCTTATGCAGTGCATCGAAACCTTTT 780

Qy        781 GCTTGGGGATGTGCTTGGAGAGGCAGATAACGCTGAAGCAGGCCTCTCATGACCCAGGAA 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        781 GCTTGGGGATGTGCTTGGAGAGGCAGATAACGCTGAAGCAGGCCTCTCATGACCCAGGAA 840

Qy        841 GGCCGGGGTGGATCCCTCTTTGTGTTGTAGTCCATGCTATTAAAAGTGTGGCCCACAGAC 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        841 GGCCGGGGTGGATCCCTCTTTGTGTTGTAGTCCATGCTATTAAAAGTGTGGCCCACAGAC 900

Qy        901 CAAGAGCCTCAACATTTCCTAGAGCCTTATTAGAAATGCAGAATCTGAAGCCCCACTCTG 960
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        901 CAAGAGCCTCAACATTTCCTAGAGCCTTATTAGAAATGCAGAATCTGAAGCCCCACTCTG 960

Qy        961 GACCCAGGACATTTTGATGAGATCCAAAGGAGTTGTATGCACATGAAAGTTTGAGAAGCA 1020
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        961 GACCCAGGACATTTTGATGAGATCCAAAGGAGTTGTATGCACATGAAAGTTTGAGAAGCA 1020

Qy       1021 TCATCATAGAGAAGTAAACATCACACCCAACTTCCTTATCTTTCCAGTGGCTAAACCACT 1080
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1021 TCATCATAGAGAAGTAAACATCACACCCAACTTCCTTATCTTTCCAGTGGCTAAACCACT 1080

Qy       1081 TAACCTCTCTGGGTGTTACCTGCTCATTTGTTTA 1114
              |||||||||||||||||||||||||||||||||
Db       1081 TAACCTCTCTGGGTGTTACCTGCTCATTTGTTTA 1114
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Response to arguments

Applicant's arguments presented 10/31/2008 traversing the rejection over Bailleul, Tuschl, Shi, and Hannon are unclear. Applicant appears to argue the applied references teach hairpin RNAs only, not double stranded iRNAs. However, Tuschl et al. clearly taught chemically synthesized 21-nucleotide short interfering RNAs composed of two separate strands for inhibiting the expression of any known mammalian gene. Shi et al. amplify the original disclosure of Tuschl et al., showing that interfering RNA may also be expressed endogenously in the form of a short hairpin RNA, which like its non-hairpin counterpart, effectively inhibits gene

expression in a mammalian cell. Accordingly, the rejection is maintained for the reasons stated above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Examiner, Art Unit 1635
December 23, 2008